K001364

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510(k) SUMMARY

SUBMITTED BY: BECTON, DICKINSON AND COMPANY
BD BIOSCIENCES
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SPARKS, MD 21152

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DATE PREPARED: June 12, 2000

DEVICE TRADE NAME: BD Directigen™ Flu A+B

PREDICATE DEVICES: Directigen™ Flu A
Biostar® AB FLU OIA®

DEVICE CLASSIFICATION: 21 CFR§866.3330
Influenza virus serological reagents

INTENDED USE: The Directigen™ Flu A+B Test is a rapid *in vitro* enzyme immunoassay (EIA) membrane test for the direct and qualitative detection of influenza A and B viral antigens from nasopharyngeal wash, nasopharyngeal aspirate, nasopharyngeal swab, lower nasal swab, throat swab and bronchoalveolar lavage specimens of symptomatic patients. The Directigen Flu A+B Test is a differentiated test, and therefore influenza A viral antigens can be distinguished from influenza B viral antigens in a single test. The test is to be used as an aid in the diagnosis of influenza A and B viral infections. Negative test results should be confirmed by cell culture. The Directigen Flu A+B Test is not intended for detection of influenza C.

DEVICE DESCRIPTION:

The BD Directigen™ Flu A+B rapid (EIA) immunoassay utilizes enzyme conjugates as the detection method and enzymatic color development to test for the presence of Influenza A and Influenza B antigens in symptomatic patient specimens. The test is designed to detect viral nucleoproteins of Influenza A and Influenza B.

For each assay, a sample is extracted and then expelled through a filter assembly into each of two wells of the test device. As the sample passes through a flow controller, Influenza A or B antigens present in the specimen non-specifically bind to the membrane in the shape of a triangle. Each of the two wells of the device is processed with a wash step. Following the wash step, a detector containing enzyme-conjugated monoclonal antibodies specific for Influenza A is added to the well labeled "A" and detector containing enzyme-conjugated monoclonal antibodies specific for Influenza B is added to the well labeled "B". The captured Influenza antigen-antibody complex is visually detected by an enzymatic color development reaction in the shape of a triangle.

The presence of a purple triangle with a small purple dot at its center in the device well labeled "A" indicates the presence of Influenza A antigen in the specimen. The presence of a purple triangle with a small purple dot at its center in the device well labeled "B" indicates the presence of Influenza B antigen in the specimen. In some cases, a strong positive reaction will be indicated by a dark intensity purple triangle which may obscure the small purple dot at the center of the triangle.

A negative Influenza A result is indicated by the absence of a purple triangle and the presence of a small purple dot in the center of the device well labeled "A". A negative Influenza B result is indicated by the absence of a purple triangle and the presence of a small purple dot in the center of the test well labeled "B".

Each BD Directigen™ Flu A+B ColorPAC™ device contains both internal positive and negative controls. The appearance of a small purple dot at the center of wells "A" and "B" provides an internal positive procedural control that validates the immunological integrity of the device, proper reagent function and that correct test procedure was followed. The membrane area surrounding the control dot (and triangle in a positive reaction) is the internal negative procedural control. The lack of a significant color development in this background area to obscure the triangle or control dot indicates that the test has been performed correctly.

DEVICE COMPARISON:

Product Feature	BD Directigen™ Flu A+B	Directigen™ Flu A	BioStar® AB FLU OIA®
Intended Use	The Directigen™ Flu A+B Test is a rapid *in vitro* enzyme immunoassay (EIA) membrane test for the direct and qualitative detection of influenza A and B viral antigens from nasopharyngeal wash, nasopharyngeal aspirate, nasopharyngeal swab, lower nasal swab, throat swab and bronchoalveolar lavage specimens of symptomatic patients.	The Directigen™ Flu A Test is an *in vitro* enzyme immunoassay membrane test for the direct rapid and qualitative detection of influenza A antigen from suitable specimens of symptomatic patients.	The BioStar® FLU OIA® assay is an Optical Immunoassay test for the qualitative, rapid detection of influenza A and B viral antigen (nucleoprotein) from nasal aspirate, nasopharyngeal swab, throat swab, or sputum specimens.
Specimen types	nasopharyngeal washes, nasopharyngeal swabs, nasopharyngeal aspirates, throat swabs, lower nasal swabs, and bronchoalveolar lavages	nasopharyngeal washes, nasopharyngeal swabs, nasopharyngeal aspirates, pharyngeal swabs	Nasal aspirates, nasopharyngeal swabs, throat swabs and sputums
Technology	EIA (enzyme immunoassay)	EIA (enzyme immunoassay)	OIA (optical immunoassay)
Detection Method	Detects the presence of nucleoprotein antigens of Influenza A & Influenza B.	Detects the presence of nucleoprotein antigens of Influenza A.	Detects the presence of nucleoprotein antigens of Influenza A & Influenza B.
Detection of Influenza virus	Differentiated detection of Influenza A and Influenza B	Detection of Influenza A only	Non-differentiated detection of Influenza A and Influenza B

NOTE: Performance of the Directigen™ Flu A+B product was established versus cell culture.

SUMMARY OF PERFORMANCE DATA:

ANALYTICAL STUDIES:

Analytical Sensitivity

Analytical sensitivity was evaluated using 13 influenza strains: seven Influenza A and six Influenza B. Serial dilutions prepared using qualified media were tested in triplicate according to the Directigen™ Flu A+B Test Procedure in the Package Insert. Viral detection limits were calculated by logistic regression analysis based on viral concentrations and interpretation on test results.

Viral Strain	Viral Type	Detection Limit ($CEID_{50}$/ml)
A/PR/8/34 (H1N1)	A	8.2×10^3
A1/FM/1/47 (H1N1)	A	5.9×10^2
A/NWS/33 (H1N1)	A	1.6×10^2
A1/Denver/1/57 (H1N1)	A	6.5×10^1
A/Port Chalmers/1/73 (H3N2)	A	2.9×10^2
A/Victoria/3/73 (H3N2)	A	3.3×10^4
A/New Jersey/8/76 (H1N1)	A	2.1×10^2
B/Lee/40	B	1.2×10^6
B/Allen/45	B	1.8×10^2
B/Maryland/1/59	B	4.6×10^1
B/GL/1739/54	B	2.5×10^3
B/Taiwan/2/62	B	6.6×10^2
B/Hong Kong/5/72	B	2.3×10^3

Influenza A and Influenza B Reactivity

Directigen™ Flu A+B was tested to demonstrate reactivity with human and non-human strains of Influenza A and B. The following strains were all detected and correctly identified as Influenza A or Influenza B using the Directigen™ Flu A+B kit:

Viral Strain	Strain source
A/PR/8/34	Human
A1/FM/1/47	Human
A/NWS/33	Human
A1/Denver/1/57	Human
A/New Jersey/8/76 (Hsw N1)	Human
A/HongKong/9821/2000	Human
A/HongKong/2997/98	Human
A/HongKong/5405/2000	Human

Viral Strain	Strain source
A/HongKong/6611/2000	Human
A/HongKong/15946/2000	Human
A/HongKong/16051/2000	Human
A/Port CHAlmers/1/73	Human
A/Victoria/3/73	Human
A/HongKong/114313/2000	Human
A/HongKong/117393/2000	Human
A/HongKong/114591/2000	Human
A/HongKong/119563/2000	Human
A/HongKong/120277/2000	Human
A/Hong Kong/68012/2000	Human
A/Human/HongKong/481/97	Human
A/Human/HongKong/482/97	Human
A/Human/HongKong/228156/97	Human
A/Human/HongKong/229540/97	Human
A/Human/HongKong/242095/97	Human
A/Human/HongKong/1073/99	Human
A/Human/HongKong/1074/97	Human
B/Lee/40	Human
B/Allen/45	Human
B/GL/1739/54	Human
B/Taiwan/2/62	Human
B/Maryland/1/59	Human
B/HongKong/5/72	Human
B/Hong Kong/28637/2000	Human
B/Hong Kong/27254/2000	Human
B/Hong Kong/28636/2000	Human
B/Hong Kong/29130/2000	Human
B/Hong Kong/29276/2000	Human
B/Hong Kong/35952/2000	Human
A/Turkey/Kansas/4880/80	Animal
A/Asia/57	Animal
A/Mallard/New York/6750/78	Animal
A/swine/HongKong/5212/99	Animal
A/Turkey/England/69	Animal
A/Duck/HongKong/477/78	Animal
A/Chicken/Alabama/75	Animal
A/Turkey/Wisconsin/68	Animal
A/Goose/HongKong/38/79	Animal
A/Turkey/Canada/63	Animal
A/Turkey/Oregon/71	Animal
A/Duck/HongKong/47/76	Animal
A/Turkey/Ontario/6118/67	Animal

Viral Strain	Strain source
A/Chicken/HongKong/G9/97	Animal
A/Swine/HongKong/9/98	Animal
A/Turkey/Wisconsin/66	Animal
A/Quail/HongKong/G1/97	Animal
A/Duck/HongKong/865/80	Animal
A/Chicken/Germany/N/49	Animal
A/Duck/Memphis/546/74	Animal
A/Duck/Alberta/60/76	Animal
A/Gull/MD/704/77	Animal
A/Mallard/Gurjev/263/82	Animal
A/Shearwater/WA/2576/79	Animal

Cross Reactivity

A panel of microorganisms (including bacteria, yeast and viruses) were cultured and tested at appropriate concentrations in triplicate with the Directigen™ Flu A+B test. None of the microorganisms tested in the panel gave a positive result in the Flu A+B test.

Interfering Substances

A variety of substances were tested with the Directigen™ Flu A+B test at concentration levels comparable to or greater than levels that may be present in patient respiratory samples. Substances tested included blood, mouthwashes, throat drops, nasal sprays, cold medications and prescription medications. Each substance was tested in triplicate either in the presence of Influenza A or the presence of Influenza B with the Directigen™ Flu A+B test. None of the substances evaluated in the presence of Influenza A gave a positive Flu B test result. None of the substances evaluated in the presence of Influenza B gave a positive Flu A test result. For all substances tested, positive results were noted for Flu A in the presence of Influenza A as well as for Flu B in the presence of Influenza B.

CLINICAL STUDIES:

Performance characteristics for the Directigen™ Flu A+B test were established in a study involving six geographically diverse clinical sites and two physician office laboratories. The study included 1262 specimens consisting of nasopharyngeal aspirates, nasopharyngeal washes, nasopharygeal swabs, lower nasal swabs, nose/throat swabs, throat swabs and bronchoalveolar lavages. At one clinical site, both nasopharyngeal swabs and lower nasal swabs were collected from each of 216 patients.

The specimen populations included 58 frozen archived specimens consisting of pre-selected influenza A positive, influenza B positive and influenza A/B negative samples. The following tests were performed on each specimen: Directigen™ Flu A+B, cell culture and direct specimen DFA.

Cell Culture

For cell culture, a portion of the specimen was inoculated into Rhesus Monkey Kidney (RMK) or Madin-Darby Canine Kidney (MDCK) cells. Cells were examined for the appearance of cytopathic effects (CPE). Any infected cells were confirmed for influenza A or B by direct fluorescent antibody (DFA) staining. Specimens negative at fourteen days were stained for negative confirmation by DFA.

Direct Specimen DFA

For direct specimen DFA testing, a portion of each specimen was used to prepare a smear for examination by direct fluorescent antibody to influenza A and B.

RT-PCR

RT-PCR was performed on all available archived specimens that were culture negative and direct specimen DFA positive. In addition, a subset of specimens with other combinations of results was evaluated by RT-PCR.

Clinical Accuracy

For all specimens evaluated, the overall sensitivity of the Directigen Flu A+B test for influenza A when compared to culture was 86.2% and for influenza B was 80.8%. The overall specificity for influenza A when compared to culture was 90.7% and for influenza B was 99.5%. For influenza A, there were 96 samples that were culture negative, Directigen positive. Direct specimen DFA was positive for 77 of the 96 samples. RT-PCR was performed on 86 of the 96 specimens; a total of 78 specimens were positive by RT-PCR. The uninterpretable rate for the Directigen Flu A+B test was 0.08% for both influenza A and influenza B results.

Nasopharyngeal Aspirates (NPA)
n=350 (one uninterpretable Directigen result is not included in the table nor in estimating performance characteristics)

		Cell Culture Results		
		A+/B-	A-/B+	A-/B-
Directigen Flu A+B	A+/B-	44	0	26*
	A-/B+	0	28	6**
	A-/B-	2	4	239

				95% C.I.
Influenza A	Sensitivity	95.7%	44/46	85.2-99.5
	Specificity	91.4%	277/303	87.6-94.3
Influenza B	Sensitivity	87.5%	28/32	71.0-96.5
	Specificity	98.1%	311/317	95.9-99.3

*Of the 26 specimens, 20/26 were positive by DFA and 23/25 were positive by RT-PCR.
**Of the 6 specimens, 6/6 were negative by DFA and 5/5 were negative by RT-PCR.

Nasopharyngeal Specimen (NP) includes: Nasopharyngeal Wash and/or Nasopharyngeal Swab
n=512

		Cell Culture Results		
		A+/B-	A-/B+	A-/B-
Directigen Flu A+B	A+/B-	100	0	41*
	A-/B+	0	12**	0
	A-/B-	13	5**	341

				95% C.I.
Influenza A	Sensitivity	88.5%	100/113	81.1-93.7
	Specificity	89.7%	358/399	86.3-92.5
Influenza B	Sensitivity	70.6%	12/17	44.0-89.7
	Specificity	100%	495/495	99.3-100

*Of the 41 specimens, 32/41 were positive by DFA and 30/35 were positive by RT-PCR.
** Frozen (archived) specimens for influenza B.

Note: Of the 50 frozen archived specimens tested, 10/13 culture positives specimens were positive and 37/37 culture negative specimens were negative for influenza A using the Directigen Flu A+ B test. For influenza B, 12/17 culture positive specimens were positive and 33/33 culture negative specimens were negative when tested with the Directigen Flu A+B test.

Nose/Throat Specimens (NTS) include: Throat Swabs (TS) and /or Lower Nasal Swabs (LNS)
n=389

		Cell Culture Results		
		A+/B-	A-/B+	A-/B-
Directigen Flu A+B	A+/B-	56	0	29*
	A-/B+	0	0	0
	A-/B-	17	1**	286

				95% C.I.
Influenza A	Sensitivity	76.7%	56/73	65.4-85.8
	Specificity	90.8%	287/316	87.1-93.8
Influenza B	Sensitivity	0.0%	0/1	0.0-97.5
	Specificity	100.0%	388/388	99.1-100

*Of the 29 specimens, 25/29 were positive by DFA and 25/26 were positive by RT-PCR.
**Frozen (archived) specimens for influenza B.

Note: Of the 5 frozen archived specimens tested, 3/3 culture positive specimens were positive and 2/2 culture negative specimens were negative for influenza A using the Directigen Flu A+ B test. For influenza B, 0/1 culture positive specimens were positive and 4/4 culture negative specimens were negative when tested with the Directigen Flu A+B test.

Bronchoalveolar Lavage (BAL)
n=11

		Cell Culture Results		
		A+/B-	A-/B+	A-/B-
Directigen Flu A+B	A+/B-	0	0	0
	A-/B+	0	2*	0
	A-/B-	0	0	9

				95% C.I.
Influenza A	Sensitivity	N/A**	N/A**	N/A**
	Specificity	100%	11/11	71.5-100
Influenza B	Sensitivity	100%	2/2	15.8-100
	Specificity	100%	9/9	66.4-100

*Frozen (archived) specimens for influenza B.
**Not applicable

Note: Of the 3 frozen archived specimens tested, 3/3 culture negative specimens were negative for influenza A using the Directigen Flu A+ B test. For influenza B, 2/2 culture positive specimens were positive and 1/1 culture negative specimens were negative when tested with the Directigen Flu A+B test.

At one clinical site, both nasopharyngeal swabs and lower nasal swabs were collected from each of 216 patients. All of the specimens from this site were negative for influenza B by both culture and the Directigen Flu A+B test. There were no statistically significant differences detected between specimen types for either the Directigen Flu A+B test (% Agreement = 206/216 = 95.4%) or cell culture (% Agreement = 200/216 = 92.6%).

Overall performance of the Directigen™ Flu A+B, is substantially equivalent[1] to viral cell culture and DFA test that were in use prior to May 28, 1976 and to the Becton Dickinson Directigen™ Flu A and the BioStar AB Flu OIA test.

[1] The term "substantial equivalence" as used in this 510(k) notification is limited to the definition of substantial equivalence as found in the Federal Food, Drug and Cosmetic Act, as amended and as applied under 21 CFR 807, Subpart E under which a device can be marketed without pre-market approval or reclassification. A determination of substantial equivalency under this notification is not intended to have any bearing whatsoever on the resolution of patent infringement suits or any other patent matters. No statements related to, or in support of substantial equivalence herein shall be construed as an admission against interest under the US Patent Laws or their application by the courts.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

JUN 2 8 2000

Ms. Monica Giguere, RAC
Regulatory Affairs Specialist
Becton, Dickinson and Company
BD Biosciences
PO Box 999
Sparks, Maryland 21152-0999

Re: K001364
Trade Name: BD Directigen™ Flu A+B
Regulatory Class: I
Product Code: GNW
Dated: June 12, 2000
Received: June 14, 2000

Dear Ms. Giguere:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4588. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its internet address "http://www.fda.gov/cdrh/dsma/dsmamain.html".

Sincerely yours,

Steven Gutman

Steven I. Gutman, M.D., M.B.A.
Director
Division of Clinical Laboratory Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

510(k) Number (if known): _____

Device Name: BD Directigen™ Flu A+B

Indications for Use:

The Directigen™ Flu A+B Test is a rapid *in vitro* enzyme immunoassay (EIA) membrane test for the direct and qualitative detection of influenza A and B viral antigens from nasopharyngeal wash, nasopharyngeal aspirate, nasopharyngeal swab, lower nasal swab, throat swab and bronchoalveolar lavage specimens of symptomatic patients. The Directigen Flu A+B Test is a differentiated test, and therefore influenza A viral antigens can be distinguished from influenza B viral antigens in a single test. The test is to be used as an aid in the diagnosis of influenza A and B viral infections. Negative test results should be confirmed by cell culture. The Directigen Flu A+B Test is not intended for detection of influenza C.

Woody Dubois

(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K001364

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use ✓
Per 21 CFR 801.109

OR

Over-The-Counter Use ___
(Optional Format 1-2-96)